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Original Research

# Efficacy and safety of single-agent pan-human epidermal growth factor receptor (HER) inhibitor dacomitinib in locally advanced unresectable or metastatic skin squamous cell cancer

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**Abstract** ***Background:*** In recurrent or metastatic (R/M) skin squamous cell cancer (sSCC) not amenable to radiotherapy (RT) or surgery, chemotherapy (CT) has a palliative intent and limited clinical responses. The role of oral pan-HER inhibitor dacomitinib in this setting was investigated within a clinical trial.
***Methods:*** Patients with diagnosis of R/M sSCC were treated. Dacomitinib was started at a dose of 30 mg daily (QD) for 15 d, followed by 45 mg QD. Primary end-point was response rate (RR). Tumour samples were analysed through next-generation sequencing using a custom panel targeting 36 genes associated with sSCC.
***Results:*** Forty-two patients (33 men; median age 77 years) were treated. Most (86%) received previous treatments consisting in surgery (86%), RT (50%) and CT (14%). RR was 28% (2% complete response; 26% partial response), disease control rate was 86%. Median progression-free

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survival and overall survival were 6 and 11 months, respectively. Most patients (93%) experienced at least one adverse event (AE): diarrhoea, skin rash (71% each), fatigue (36%) and mucositis (31%); AEs grade 3–4 occurred in 36% of pts. In 16% of cases, treatment was discontinued because of drug-related toxicity. *TP53*, *NOTCH1/2*, *KMT2C/D*, *FAT1* and *HER4* were the most frequently mutated genes. *BRAF*, *NRAS* and *HRAS* mutations were more frequent in non-responders, and *KMT2C* and *CASP8* mutations were restricted to this subgroup.

***Conclusions:*** In sSCC, dacomitinib showed activity similar to what was observed with anti–epidermal growth factor receptor agents, and durable clinical benefit was observed. Safety profile was comparable to previous experiences in other cancers. Molecular pt selection could improve therapeutic ratio.



## 1. Introduction

Skin squamous cell cancer (sSCC) has shown an increased incidence in recent years (8.9–31.7 cases per 100,000 person-years in Europe) [1]. Prognosis is generally favourable, with most of the patients cured with local therapies, except from a small percentage (<10%) with distant metastasis or with recurrence not amenable to surgery or radiation. Initial lesions are most frequently (80%) localised in head and neck (H&N): metastases may occur in lymph nodes, lungs, the liver or bones [2].

Chemotherapy (CT) is reserved in case of recurrent or metastatic (R/M) disease, with palliative intent. The most commonly used drug regimens are cisplatin based [3]. Clinical responses are limited; therefore, the identification of an effective treatment for R/M sSCC is an unmet medical need.

In primary sSCC, expression of epidermal growth factor receptor (EGFR) was found in more than 80% of cases [4,5]; limited data exist about its expression in R/M disease. Primary lesions associated with subsequent metastases have been shown to more likely overexpress EGFR in comparison with not recurring lesions [6]. Even if in small studies, HER2 expression is common in sSCC [4–6] and coupled with EGFR and HER3 expression [4].

Anti-EGFR therapy in sSCC was explored in phase II trials, with cetuximab and panitumumab in unresectable/metastatic setting [7], with gefitinib in potentially curable disease [8] and in case reports [9–11]. Dacomitinib is an orally bioavailable, highly selective, second-generation small-molecule inhibitor of EGFR, HER2 and HER4, that specifically and irreversibly binds to and inhibits these receptors, resulting in inhibition of proliferation and induction of apoptosis in EGFR-expressing tumour cells.

## 2. Methods

### 2.1. Patients

Inclusion criteria for enrolment in this trial were histological diagnosis of sSCC not amenable to surgical treatment with curative purposes or with clinical contraindication to surgery; measurable disease according to Response Evaluation Criteria in Solid Tumours (RECIST) 1.1; Eastern Cooperative Oncology Group (ECOG) performance status 0–2; age ≥18 years. Subjects previously treated with EGFR inhibitors were not included. The study was approved by local ethics committees of the centres, and all patients provided an informed consent.

### 2.2. Study design

This clinical study, registered in ClinicalTrial.gov (NCT02268747), was an open-label, multicentric, uncontrolled phase II trial with dacomitinib in unresectable or metastatic sSCC.

Patients started assuming dacomitinib 30 mg daily for 2 weeks, followed by 45 mg daily in case the highest skin adverse event (AE) was less than grade 2. Dose modifications were applied to manage treatment-related toxicity. The first step of dose reduction (DR) consisted in the switch from 45 to 30 mg daily, the second one from 30 to 15 mg. Resumptions of higher doses were not allowed after DR. Treatment was continued until disease progression (PD), unacceptable toxicity or any medical condition that would suggest stopping the treatment for patient's safety. Clinical assessments were performed for every 28-d cycle, tumour evaluations at baseline and every other cycle; clinical response was assessed according to RECIST 1.1.

### 2.3. Statistical methods

Primary end-point was the best response rate (RR) to dacomitinib, defined as the sum of partial response (PR) and complete response (CR) frequencies. The hypothesis was that we would consider the drug as effective and worth for further evaluation if the RR would be at least 45%, with an increase of 17% in respect to previous study with cetuximab in the same setting of disease [7] in which an RR of 28% was shown. To achieve this goal, the study was designed according to the Simon's two-stage optimal design [12] with a target activity level of